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EXPEDITED PROCEDURE - EXAMINING GROUP 1646

S/N 08/955,572 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Kwon, Byoung	Examiner: Claire Kaufman	
Serial No.:	08/955,572	Group Art Unit: 1646	
Filed:	October 22, 1997	Docket: 740.013US2	
Title:	NEW RECEPTOR AND RELATED PRODUCTS AND METHODS		

SUPPLEMENTAL RESPONSE UNDER 37 C.F.R. § 1.116

Box AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

The remarks provided herein are intended to address the Examiner's comments in the Advisory Action dated November 23, 1998.

In accordance with Rule 1.821(e), a copy of a substitute SEQUENCE LISTING in ASCII computer readable form was filed on October 26, 1998. It is certified that the contents of the paper version of the substitute SEQUENCE LISTING and the computer readable form thereof submitted on October 26, 1998 are the same. It is further submitted that the paper copy of the substitute SEQUENCE LISTING and the computer readable form of the substitute SEQUENCE LISTING do not represent new matter.

With respect to the "undue experimentation" alleged by the Examiner that would be necessary to identify the ligand binding portion of SEQ ID NO:2, the Examiner is requested to consider Armitage et al. (Eur. J. Immunol., 22, 2071 (1992)) and Miyamura et al. (J. Clin. Invest., 98, 1809 (1996)), a copy of each is submitted herewith). Armitage et al. report that they used a biotin-labeled soluble fusion protein of CD40 (CD40 is a B cell membrane protein) and the Fc region of human IgG1 (CD40.Fc) to identify a CD40 ligand on a murine thymoma cell line (i.e., T cells). Murine thymoma cells which were selected for binding to the fusion protein expressed a soluble protein that stimulated human and murine B cell proliferation, an activity which could be neutralized by preclearing the supernatants with immobilized CD40.Fc. Thus, the authors concluded that they had identified a source of membrane-bound and soluble CD40 ligand.

Miyamura et al. describe the preparation and screening of a series of deletion constructs encoding portions α-galactosidase A. Thus, it is clearly within the skill of the art worker to manipulate constructs, e.g., by deletion analyses, to identify constructs that encode a portion of a polypeptide and compare the activity of that polypeptide to the activity of the full length polypeptide. Therefore, given Applicant's disclosure of the amino acid sequence of H4-1BB, i.e., SEQ ID NO:2, and the skill of the art worker in the relevant art area, it is Applicant's position that the preparation and screening of fragments of SEQ ID NO:2 to identify regions of SEQ ID NO:2 that bind to a cell membrane ligand is well within the skill of the art.

The Examiner also asserts that the specification does not provide a reasonable expectation that a pharmaceutical composition comprising a soluble H4-1BB polypeptide which comprises the extracellular domain of SEQ ID NO:2, or a fragment thereof, in admixture with a suitable diluent, carrier or excipient (claim 26) would be effective to treat T cell-mediated immune responses. Figures 4(b)-(c) and 5(b)-(c) of the specification illustrate the interaction of 4-1BB with its ligand, and how 4-1BB can be used to suppress T cell-dependent immune responses. See also pages 17-18.

To provide further evidence that the specification, in view of the skill of the art worker in the relevant art area, enables the use of the claimed composition to treat T cell-mediated immune responses, the Examiner is requested to consider Linsley et al. (Science, 257, 792 (1992), copy enclosed). Linsley et al. disclose that B7 is a molecule on antigen presenting cells that binds to T cell surface molecules CD28 and CTLA-4 (see also Figures 4(a)-(b) and 5(a)-(b) of the specification). The binding of B7 on B cells to CD28 or CTLA-4 on T cells activates T cells. A soluble fusion protein having the extracellular domain of CTLA-4 and Ig blocked the binding of B7 to CD28. Moreover, this fusion protein suppressed T cell-dependent antibody responses *in vivo* after mice were injected with one of two different antigens.

Since 4-1BB production is induced during T cell activation, blocking the interaction of T cells with antigen presenting cells which express H4-1BB ligand by contacting cells with a polypeptide such as that recited in claim 26 will lead to immunosuppression. Thus, if the proliferation of T cells in a particular disease or pathology is excessive, the suppression of those T cells would be indicated.

It is respectfully submitted that the pending claims are in conformance with the requirements of 35 U.S.C. § 112(1). Therefore, the Examiner is requested to withdraw the § 112(1) rejection of the claims.

In the Advisory Action dated November 23, 1998, the Examiner alleges that the Rule 131 Declaration filed on October 23, 1998 was insufficient to establish a conception of the invention prior to the effective date of Schwarz et al. (GenBank Accession No: L12964). In particular, the Examiner asserts that the Rule 131 Declaration failed to provide a sufficient showing of conception of that which was disclosed in Schwarz et al., that the evidence provided with the Declaration was lacking in clarity, i.e., the photocopy of the Exhibit was too dark, and that the Declaration did not indicate that Applicant was aware of what the Exhibit showed.

Schwarz et al. disclose the nucleotide sequence encoding, and the inferred amino acid sequence of, ILA. The inferred amino acid sequence of ILA has one amino acid substitution relative to Applicant's SEQ ID NO:2. The substitution is at amino acid position 107, i.e., it is in the extracellular domain of ILA.

The Examiner is respectfully requested to consider the Supplemental Rule 131 Declaration enclosed herewith. In that Rule 131 Declaration, Applicant declares and documents that in the United States, he had conceived of isolating and purifying DNA encoding human 4-1BB prior to the April 22, 1993 publication date of Schwarz et al. Moreover, in the Declaration, Applicant declares and documents that, after conception, he proceeded diligently to reduce the invention to practice in the United States. In particular, Applicant refers to Exhibits A, B, C, and D, attached to and incorporated by reference into the Declaration, as factual evidence of conception of the invention prior to the effective date of Schwarz et al. coupled with due diligence from conception to constructive reduction to practice.

Exhibit A is a photocopy of certain pages from U.S. application Serial No. 08/012,269, filed on February 1, 1993, an application of which Applicant is the sole inventor. U.S. application Serial No. 08/012,269 discloses the nucleotide sequence and inferred amino acid sequence of murine 4-1BB (page 17, and Figures 2A and 2B). At page 24, a method of isolating the human homolog of murine 4-1BB is disclosed. The preparation of a soluble form of murine 4-1BB and a murine 4-1BB fusion protein is described at pages 29 and 70, respectively. The

introduction of a construct encoding soluble murine 4-1BB into host cells, and the subsequent purification of soluble murine 4-1BB, is disclosed at page 29.

Therefore, prior to the effective date of Schwarz et al., Applicant had prepared recombinant murine 4-1BB polypeptide, including a soluble, murine 4-1BB fusion polypeptide. Moreover, Applicant had envisioned methods to isolate the human homolog of murine 4-1BB, an obvious variation of murine 4-1BB.

Exhibit B and Exhibit C are each a photocopy of an autoradiogram. Various combinations of degenerate primers (such as those described at pages 14-15 of the present specification which are complementary to nucleotide sequences in the extracellular domain of 4-1BB) and human lymphocytic RNA were employed in a reverse transcriptase-polymerase chain reaction to obtain amplification products that corresponded to the human homolog of murine 4-1BB. The DNA products were separated on agarose gels and DNA isolated from individual bands. The isolated DNAs were subjected to Southern blot analysis using a radiolabeled murine 4-1BB DNA probe under low stringency conditions, the results of which were recorded on an autoradiogram (Exhibit B). The DNA in the hybridizing band in lane 7 of Exhibit B was cloned and then subjected to Southern blot analysis using radiolabeled murine 4-1BB DNA, the results of which were recorded on another autoradiogram (Exhibit C). Exhibit C is dated prior to the effective date of Schwarz et al.

Thus, the combination of Exhibits A, B, and C evidence Applicant's conception of the invention prior to the effective date of Schwarz et al.

Exhibit D demonstrates that the invention disclosed in Exhibits A, B and C was diligently pursued from a time before the effective date of Schwarz et al., i.e., April 22, 1993, to a time approximately five months after the effective date of Schwarz et al., at which time the invention was constructively reduced to practice, i.e., by the filing of the parent application to the present application.

The Examiner is respectfully reminded that Applicant need demonstrate only so much of the claimed invention as taught by the prior art reference, or what is obvious in view of the reference. In re Stempel, 113 U.S.P.Q. 77 (C.C.P.A. 1957). Thus, the enclosed Rule 131 Declaration properly establishes Applicant's date of invention as earlier than the effective date of Schwarz et al. Therefore, Schwarz et al. cannot be used to support a rejection of the claims under

35 U.S.C. § 103(a), and so the Examiner is respectfully requested to withdraw the § 103(a) rejection of the claims.

Applicant respectfully asserts that the enclosed supporting documents and Rule 131 Declaration place the application in better form for appeal by materially reducing or simplifying the issues for appeal. Therefore, consideration is appropriate and is respectfully requested.

The Examiner is invited to telephone the below-signed attorney at (612) 373-6959 to discuss any questions which may remain with respect to the present application.

Respectfully submitted,

By his Representatives,

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Date February 26, 1999 By _____

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Box AF, Assistant Commissioner for Patents, Washington, D.C. 20231, on this 26 day of February, 1998.

Dawn M. Poole
Name

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Signature